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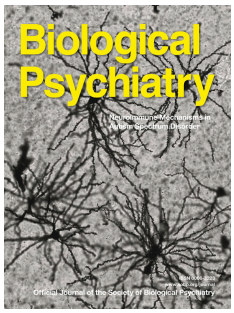

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Programming Bugs:
Microbiota and the Developmental Origins of Brain Health and Disease

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Abstract

It is almost thirty years since Barker first highlighted the importance of prenatal factors in contributing to the developmental origins of adult disease. This concept was later broadened to include postnatal events. It is clear that the interaction between genetic predisposition and early life environmental exposures are key in this regard. However, recent research has also identified another important factor in the microbiota, the trillions of microorganisms that inhabit key body niches including the vagina and gastrointestinal tract. Since the composition of these maternal microbiome sites have been linked to maternal metabolism and are also vertically transmitted to offspring, changes in the maternal microbiota are poised to significantly impact on the newborn. In fact, several lines of evidence show that the gut microbiota interacts with diet, drugs and stress both prenatally and postnatally and that these exogenous factors could also impact the dynamic changes in the microbiota composition occurring during pregnancy. Animal models have shown great utility in illuminating how these disruptions result in behavioral and brain morphological phenotypes reminiscent of psychiatric disorders (anxiety, depression, schizophrenia, autism-spectrum disorders). Increasing evidence points to critical interactions between the microbiota, host genetics and both the prenatal and postnatal environment to temporally program susceptibility to psychiatric disorders later in life. Sex-specific phenotypes may be programmed through the influence of the microbiota on the hypothalamic-pituitary-adrenal axis and neuroimmune system.

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1.0 Building on Barker: Four Hit Hypothesis for Development of Disease

Studies on the developmental origins of health and disease have gleaned mechanistic insights as well as risk factors that impact development. Using large cohort studies, Dr. David Barker showed that low birth weight was a risk factor for cardiac disease and ischemia (1-4). He postulated that factors affecting the fetus, pre- and early postnatal environment, and genetic predisposition, programmed health and disease in adulthood (1-4). Disruptions of any of these factors will function as a "hit" towards disease, and multiple "hits" may interact and increase the magnitude of impact of these factors. Current research in neuroscience, physiology and immunology has now shown that the human microbiota, referring to the individual microorganisms, and the microbiome, their collective genomes (5-7), play an important role in health and disease; thus the microbiota could act as a fourth "hit". The gut and vaginal microbiota is both affected by, and can act upon, these other factors in Barker's hypothesis, showing integrative functionality in the programming of health and disease (see **Figure 1**).

The vaginal and gut maternal microbiome has been a recent focus for understanding the health and disease in offspring. In fact, there is evidence of universal vertical microbiota transmission between mother and offspring in all animals (8). There is further interest in the study of the maternal microbiota to elucidate its roles in mediating the impact of prenatal factors, such as diet and pharmacological agents, on the offspring. During early development, the infant microbiota may also be vulnerable to shaping from similar postnatal exposures. Thus, one of the emerging questions in developmental psychopathology research is how might the maternal vaginal and gut microbiota interact with prenatal and postnatal environment, and host genetics to program brain health and disease in later life?

For the purposes of this review, the programming of brain health refers to physiological, transcriptional or epigenetic changes induced by prenatal environment or exposure to compounds that lead to altering the homeostatic set point for neurodevelopment in the first 1000 days of human life or the animal model equivalent (9). With a focus on bacteria, we describe how pregnancy-related changes in the composition of the maternal microbiota as well as changes in the microbiota during early postnatal life may interact with host genetics, prenatal and early life environment to affect brain health. During fetal development as well as early life, critical periods exist where both negative and positive interventions could alter the trajectory of neurodevelopment and impact brain health later in life (see **Figure 2**).

2.0 The Microbiota

The human gut microbiota, consisting of trillions of bacteria and weighing approximately 400 grams (10), and their genomes, have profound impact on physiology and behavior. It is the most well-characterized mammalian microbiome and is involved in modulating intestinal barrier permeability as well as gut-brain axis signaling through the vagal nerve, inflammatory molecules, endocrine molecules, and microbial metabolites (11-14). The brain-gut-microbiota axis includes components of the central nervous system, the neuroendocrine and neuroimmune systems as well as components of the autonomic and enteric nervous system (15). However, many of the mechanisms underlying this axis remain unknown.

Other areas of the body which host a bacterial community include the skin, oral cavity, conjunctiva, lungs, biliary duct, the vagina and possibly the placenta. During pregnancy, the communities in many body areas change, but most focus has been placed on the remodeling that takes place in the gut and the vagina of the mother. To assess these changes, diversity is used to

determine the amount of different types of bacteria as well as their relative abundances within a community.

2.1 Human Microbiota During Pregnancy

2.1.1 Gut Microbiota

During pregnancy, the human gut microbiome undergoes dynamic compositional changes, which accompany changes in metabolism (16-19). As gestation progresses, intestinal microbiota diversity, and specifically Proteobacteria and Actinobacteria increase (17). As a result, the gut microbiota composition during the third trimester is significantly different from its composition at the beginning of pregnancy (17). Gut microbial diversity has also been shown to increase postpartum in the mother and vaginally-delivered newborns (17, 20, 21). Interestingly, germ-free mice that received a transplantation of human microbiota from the third trimester of pregnancy displayed symptoms of metabolic syndrome – increased adiposity, inflammation and reduced glucose tolerance (17-19). These effects may be mediated by key gut microbial metabolites such as short-chain fatty acids, which were previously shown to be associated with these metabolic changes during pregnancy (16). Since most changes in the gut microbiota occur in the second and third trimester, perhaps microbiota modulation during these critical time periods can impact neurodevelopment.

2.1.2 Vaginal Microbiota

The human vaginal microbiome consists of multiple stable community state types, which destabilize during pregnancy (22, 23). It is most abundant in *Lactobacillus spp.* before pregnancy, but this species may be reduced during pregnancy (24, 25). However, only some

studies found concurrent reduction in overall bacterial diversity during pregnancy (26) while others did not (24, 25). In addition, postpartum bacterial diversity was found to be increased (25) Notably, there are also differences in the composition of the vaginal microbiome during pregnancy and postpartum between different ethnic groups suggesting an interaction between bacterial colonization and host genetics and environment (25). The infant gut microbiome most closely resembles the vaginal microbiome of the mother, which initially colonize the infant, consistent with patterns of vertical transmission across the animal kingdom (8, 27, 28).

2.2 Pregnancy Related Changes in the Microbiota: Preclinical Models

2.2.1 Intestinal Microbiota

The intestinal microbiota in mouse models also undergoes compositional changes during pregnancy, affecting maternal metabolism. While taxa from the Firmicutes and Tenericute phyla decrease in composition (29, 30), there is an increase in the circulation of short-chain fatty acids produced by other members of the microbiota along with tissue-specific transcriptional changes in its receptor, free fatty acid receptor 2 (29). Interestingly, mice deficient in this receptor experienced hyperglycemia and decreased insulin secretion (29).

2.2.2 Vaginal Microbiota

There is also evidence of changes in the vaginal microbiota composition in mice during pregnancy. Diversity of the bacterial community actually increased during early gestation and then decreased early postpartum (31), a finding disparate with human studies (see 2.1.2). In addition, the gut microbiota of the offspring resembled the maternal vaginal microbiota in early postnatal life and at weaning it more resembled that of the maternal gut microbiota (31).

3.0 Host Genetics and the Microbiome

To our knowledge there are currently no investigations into the interactions between host genetics and the microbiome during pregnancy or in offspring during early postnatal development in preclinical models. There is conflicting evidence regarding the role of host genetics in human and mouse gut microbiota colonization and composition (32-34).

4.0 Prenatal Environment and the Microbiota

Although it is commonly thought that initial gut colonization occurs at birth during vaginal delivery, there is some albeit controversial evidence of a prenatal microbiome (35, 36). Bacteria have been isolated from human meconium, stool that forms in the fetus before birth, and others have found morphological and sequencing evidence of a placental microbiome resembling the oral microbiome (37-40). Although a placental microbiome may not necessarily be transferred to the fetus *in utero*, it may be involved in fetal development. However, placental colonization might occur during labor due to ruptures in the placental barrier (35). Although bacteria have been isolated from the umbilical cord of infants born by umbilical Caesarean section (41) many of these studies have been criticized due to a lack of proper controls for contamination, evidence of viable bacteria rather than finding evidence of bacterial genes through sequencing, or inappropriate molecular approaches to detect the bacteria (36). The existence of germ-free mouse models is also further evidence against the prenatal microbiome (36). However, it is clear that a number of factors can influence the maternal microbiome in pregnancy that can either directly or indirectly affect the developing fetal brain.

4.1 Drugs and the Microbiota

Over a quarter of pharmaceutical drugs have been shown to impact the composition of the microbiota (42-45), which has been implicated in both the efficacy and side effects of these

drugs (46). See **Table 1** for more details on the impact of prescription drugs on the microbiota and behavior of offspring. However, there are few studies investigating the prenatal effect of drugs on the microbiota.

4.1.1 Antibiotics

Antibiotics are the most commonly prescribed drug during pregnancy (47), and reduce the diversity and bacterial load of the microbiome through bactericidal or bacteriostatic actions. Succinyl sulfa thiazole administration during pregnancy in rats caused sex-specific impairments social behavior of the offspring as well as impairments in pre-pulse inhibition – an endophenotype of schizophrenia (43). A combination of non-absorbable antibiotics, administered to mice during pregnancy, reduced exploratory behavior in their offspring (48). This is further validated by germ-free mouse models, which display social impairments as well as abnormal microglial development (12, 49, 50). Microglia have recently been shown to play an important role in neurodevelopment (51). Accordingly, sex-specific aspects of microglial activation which persisted in adulthood in germ-free mice may contribute to the sex biases in psychiatric disorders in later life (50).

4.1.2 Antidepressants

Different classes of antidepressant drugs including tricyclic antidepressants (52) and selective serotonin inhibitors (53), as well as ketamine (54) which may be used in the future as a new treatment, impact the growth of bacteria. It is unclear if their bacteriocidal/bacteriostatic actions impact their efficacy. Prenatal exposure to selective serotonin reuptake inhibitors induces anxiety-like and depressive-like behavior in adulthood (55) in rodents, though the implications of these results for humans are still being discussed (56). In addition, evidence suggests that these

drugs may impact birth weight and motor development in humans, as well as in animal models (57); however potential mechanisms are unknown. Due to the prevalence of antidepressant administration during pregnancy (58), it is crucial to characterize the interaction between maternal mental health, antidepressant administration and the offspring's microbiota and mental health.

4.1.3 Drugs of Abuse

The impact of several substances of abuse on the microbiome have not yet been conducted. In rodents, ethanol (59-61) and cocaine exposure (62) have shown effects on the gut microbiota composition. In humans, alcohol exposure during pregnancy leads to the development of fetal alcohol spectrum disorders (63). The severity of these effects on the brain may however supersede its impact from changes in the maternal microbiota. Future studies should identify if different gut microbiota compositions are more susceptible to the effects of these substances during pregnancy, as well as their impacts on the newborn.

4.1.4 Valproate/Valproic Acid

Valproate is an anti-epileptic and mood stabilizer but is also a known teratogen; exposure during gestation results in a 4% risk in autism-spectrum disorder (64) and has been able to produce autistic endophenotypes in prenatally exposed rodents (44, 65, 66). Valproic acid increased the Firmicutes/Bacteroidetes ratio and altered caecal butyrate in the gut microbiota of the male offspring (44). However, these changes likely involves its activity as a histone deacetylase inhibitor (67) rather than its anti-epileptic mechanism (see which may involve voltage-dependent sodium channels and the gamma-aminobutyric acid system (68)). Other pharmaceutical drugs may also alter the gut microbiota through secondary mechanisms of action.

4.2 Maternal Diet and the Microbiome

4.2.1 Unhealthy diet

Unhealthy diet in humans leads to obesity and poor cardiovascular health but recent research has also shown its impact on neurocognitive development in both humans and rodents (69). Common rodent models of unhealthy diet include high-fat diet (36-60 % kcal from fat), Western diet (high fat and high sugar) as well as diets focusing on specific types of fats. Some of these studies have been criticized because improper controls are often selected and may introduce confounds that complicate the interpretation of admittedly intriguing results (70, 71). A maternal high-fat diet in mice resulted in higher-fold increases in abundance of bacteria in the gut microbiome of the mother during pregnancy, and differences in compositional changes compared to animals fed a control diet (30). In addition, both prenatal and adolescent exposure to a high fat diet changed the gut metabolome and microbiota composition in mouse, rat and macaques (30, 72-74). Prenatal Western diet has also been shown to alter the gut microbiota composition leading to an increased Firmicutes/Bacteroidetes ratio as well as sex-specific differences in colonic gene expression (75). Although the impact of prenatal trans-fatty acid exposure on the microbiota has not been determined, it can alter hypothalamic function of prenatally exposed rodents in adulthood (76). Furthermore, unhealthy diets during pregnancy in mice also lead to sex-specific differences in gene expression (77, 78), social deficits (73, 78), altered hypothalamic stress response (79) and inflammation (79, 80) in the offspring (see Table 2). This suggests that a greater emphasis should be placed on nutrition during pregnancy, though it is unclear if these changes in maternal microbiota directly impact the stress response in human infants.

4.2.2 Omega-3 Polyunsaturated Fatty Acids

Several nutrients may play a positive role in neurodevelopment and microbiota maturation. A high-fat diet supplemented with omega-3 polyunsaturated fatty acids increased the diversity of microbiota and enriched *Bifidobacterium* at a species level (81). Omega-3 intake during pregnancy regulated the hypothalamic-pituitary-adrenal (HPA) axis activity, shifted the maternal stress-induced gut microbiota composition to be more similar to an unstressed composition and conferred resilience to stress later in life; in contrast, a deficit in omega-3 polyunsaturated fatty acids affected the metabolome, impaired communication and social behavior, while increasing depressive-like behavior (82-85).

4.2.3 Prebiotics

Prebiotics promote the growth of beneficial bacteria and include indigestible fibers that are fermented by colonic bacteria to produce short-chain fatty acids and provide a health benefit, though their effects on neurodevelopment have not been well studied (86). Administration of the prebiotics galactooligosaccharide and inulin in mice reduced immune activation and intestinal permeability in offspring through gut microbiota modulation (87). The prenatal administration of caprine milk oligosaccharide in mice has been shown to increase Bifidobacteria and butyric acid in the offspring colon (88). Interestingly, the addition of inulin to a mouse maternal high-fat diet abrogated the negative metabolic effects of the high-fat diet on offspring (89).

4.2.4 Probiotics

Probiotics are beneficial strains of bacteria that confer a health benefit to the host. Administration during pregnancy in humans can reduce the risk of atopy but not other immunity-related diseases like asthma (90, 91), however, many current supplements lack proof of

effectiveness (92) . Although there is a lack of research on the prenatal impact of probiotics within our current scope, several studies have investigated the effects of postnatal administration of probiotics for improving psychiatric symptoms (i.e. anxiety or autism-spectrum disorder-like; see 6.2.4). It is evident that more animal and human research must be conducted to determine the impact of prenatal probiotics on the maternal and offspring microbiota.

4.3 Maternal Stress

Maternal stress is modulated by the HPA axis and has been shown to impact this axis in the offspring. In offspring, maternal stress has increased serum levels of corticosterone, increased anxiety, social impairment and altered the resilience of different strains of rodents (93-97). Maternal stress can also alter the gut and vaginal microbiota during pregnancy, decreasing diversity of maternal gut microbiota as well as dysregulating glucose metabolism in mice (31). Varied prenatal stress interrupted normal pregnancy-related compositional changes in the mouse vaginal microbiota and also altered the protein content in the vaginal mucosa, which may have contributed to altered abundance of Firmicutes and Bacteroidetes in their offspring's gut microbiota (98). After pregnant mice experienced restraint stress specifically, female offspring showed more anxiety-like behaviors as well as decreases in brain-derived neurotrophic factor in the placenta concurrent with later decreases of its expression in the adult amygdala (99).

In humans, ongoing maternal stress (inclusive of prenatal and postnatal stress) has been associated with mental health problems in adult offspring (100), as well as with influencing the development of the offspring microbiota over the first 110 days after birth (101). However, the mechanism by which the negative impact of maternal stress is transmitted to the offspring's microbiota is unknown, though IgA mediated immunity could be implicated (102).

4.4 Maternal Immune Activation

The maternal immune activation model is based around the controversial idea that maternal infections during pregnancy can impact psychiatric outcomes in the children (103). A rodent model of maternal immune activation commonly administers viral mimetic poly(I:C) or bacterial lipopolysaccharide to produce psychiatric endophenotypes in offspring. Specifically, the viral mimetic poly(I:C) administered at E12.5 in mice altered the gut microbiota composition and increased gut leakiness by decreasing claudin expression, while also elevating intestinal cytokine levels, including interleukin-6 in offspring (104). This model also elevated the bacterial production of, 4-ethylphenylsulfate, which induced anxiety-like symptoms in wild-type mice (104). However, there is heterogeneity in the time of administration of the viral mimetic poly(I:C) which can lead to the development of different biomarkers or behaviors common to different disorders including schizophrenia (105, 106) or autism-spectrum disorder-like behaviors in mice (107), and inconsistent depression-like endophenotypes in rats and mice (108).

Though there exists no current research of its impact on the microbiota, the bacterial mimetic lipopolysaccharide can also induce behavioral phenotypes for anxiety, depression, or autism spectrum disorder in offspring (109, 110); impairments in hippocampal development and neurogenesis (111, 112); and increased postnatal inflammation (110). In mice, lipopolysaccharide-induced maternal inflammation caused placental damage and fetal intestinal injuries that persisted in adulthood (113); further studies should focus on the potential of a placental microbiome to mediate these interactions.

5.0 Caesarean section

There are now a large number of studies showing a marked effect of mode of delivery on the gut microbiome (20, 27, 114-126), although some studies have found less of an influence than others (127). Infants born via Caesarean-section (C-section) had a gut microbiota more similar to the maternal skin microbiota than the vagina (20, 27, 114, 115), delayed *Bacteroides* colonization (114, 115), delayed *Lactobacillus* colonization (27), lower circulating chemokines (20) and a higher risk of vertical obesity transmission from their mother (126). Similar to humans, C-section mice initially had a significantly different gut microbiota from their mother (128). In addition, they had significant differences in the abundance of bacteria in the orders Clostrodiales and Bacteroidales as well as lower systemic interleukin-10 expression (128). Although the restoration of the microbiota in Caesarean born infants using a vaginal swab has been piloted, the long term consequences of such an intervention have yet to be studied (129). Alterations in the microbiota induced by C-section may play a functional role in predisposing such infants to a greater relative risk of allergy, asthma, obesity and Type 1 Diabetes (126, 130, 131). The relative contribution of such disturbances to brain health is less clear although epidemiology and animal studies are beginning to unlock some clear links (132-136).

6.0 Postnatal Environment and the Microbiota

6.1 Postnatal Drugs and the Microbiota

Few studies have assessed the impact of postnatal drugs on the microbiota and behavior (see Table 1); this section summarizes the existing literature.

6.1.1 Antibiotics

Exposure to antibiotics within the first three years of life in humans decreased microbiome stability and diversity while it transiently increased transcription of antibiotic resistant genes

(137) and increased adiposity in males during childhood (138). Moreover, neonatal exposure in rodents to antibiotics have been shown to alter the microbiota, brain inflammation and behavior (139), contribute to obesity (140), increase visceral pain receptors and sensitivity (141) . More research must be conducted to elucidate the effects of common prescriptions of early-life antibiotics on brain-health in later life.

6.1.2 Antidepressants

In humans, antidepressants have been shown to transfer through breast milk and some can reach a clinically significant concentration in the infant's serum (142), though their effects on the infant have not yet been established (143). In rodents, early postnatal exposure to selective serotonin inhibitors alters their social behavior, anxiety-like and depressive-like behaviors (144, 145). There are no studies investigating the impact of early exposure of these drugs to the gut microbiota composition.

6.1.3 Antipsychotics

Similarly, the effects of antipsychotics during breastfeeding – and whether they are able to transfer to the infant in a clinically significant concentration are currently unknown. However, antipsychotics have been shown to impact the microbiota in rats and adolescent children, leading to weight gain (45, 146, 147). It is unclear if similar effects on the microbiota occur as a result of antipsychotic transfer through breast milk, and if this interaction impacts infant neurodevelopment.

6.2 Postnatal Diet and the Microbiota

The stability and composition of the early postnatal gut microbiota community is strongly dependent on diet, evident in the microbiota differences between breastfed and formula-fed

infants (148). There are now more studies examining the impact of both healthy and unhealthy diets in early life.

6.2.1 Unhealthy Diet

An unhealthy diet commencing in early postnatal life also alters the microbiota composition (149) and results in different behavioral and inflammatory phenotypes (see Table 2). High-fat diet after weaning and during adolescence altered the HPA-axis in female rats and impaired hippocampal memory and increased hippocampal lipopolysaccharide-induced cytokine response in the males (150, 151). Meanwhile high-fat diet bingeing during adolescence in mice increased anxiety and cocaine self-administration in adulthood (152).

6.2.2 Prebiotics

Few published studies have assessed the impact of early life prebiotics administration in humans on psychiatric outcomes but have shown effects in reducing the risk of atopy, an autoimmune disease (153). In juvenile rats, inulin administered for two weeks increased basal corticosterone levels and elevated corticosterone after an anxiety-inducing stimulus, but the animals showed less anxiety in behavioral tests (154).

6.2.3 Probiotics

In humans, probiotics may reduce the risk of depression (155) and autism (156, 157). In rodents, *Lactobacillus* administration had similar effects to inulin, reducing anxiety through the HPA axis (154). Interestingly, when combined with inulin, it did not affect the corticosterone levels and increased 5-HT_{1A} receptor mRNA in the hippocampus, a receptor associated with anxiety and depression (154). Notably, *Lactobacillus rhamnosus* and *L. helveticus* administration in stressed infant rats (postnatal day 2 to 14) had a protective effect on fear conditioning memory and

relapse after extinction in early life (158). Some strains, such as *Bifidobacteria longum* and *Bifidobacteria breve*, can mediate anti-anxiety and anti-depressive behaviors in preclinical rodent models (159). In mice, *Bifidobacterium breve* combined with prebiotics in early life exerted protection from the negative metabolic effects of a Western diet (160), showing promise for co-administration of prebiotics and probiotics.

6.3 Postnatal Stress and the Microbiota

Early postnatal stress impacts the HPA-axis and contributes to the programming of brain health in later life (161). Different types of early postnatal stress (social isolation, maternal separation) alter the gut microbiota composition and metabolism in rats (162-164) and their inflammatory profiles (163, 164). Social isolation also impaired memory and learning in rats (163). Finally, germ free mice were more vulnerable to restraint stress – resulting in higher adrenocorticotropic hormone and corticosterone in plasma (165, 166), a reduction in glucocorticoid receptor mRNA and an increased stress response (165). Remarkably, these effects were rescued with microbiota transplantation during adolescence but not adulthood (165).

7.0 Sex-Specific Programming of Psychiatric Disorders Later in Life

Many psychiatric disorders differ among the sexes in terms of prevalence or onset – including autism (167), mood disorders (168), anxiety disorders (168) and schizophrenia (169). The underlying biological basis of these sex differences is still unknown. Since microbiota-related alterations have shown sex-specific effects after exposure to prenatal or postnatal environmental stimuli (44, 75, 99, 147), they may play a role in the sex-specific programming of health later in life.

The gut microbiota and its metabolites influence the development of the microglia, and in its absence, development is disrupted in a sex-specific manner (12, 49, 50). Abnormal microglial phenotypes were rescued with short-chain fatty acids, produced by certain members of the microbiota (12). The microglia are involved in synaptic pruning and maturation during neurodevelopment (see review by Salter (170)).

Other "hits" that disrupt the microbiota could prevent it from reaching a healthy homeostasis (171, 172) and result in increased inflammation. In fact, many psychiatric disorders may involve the dysregulation of the immune system – including mood disorders (173-175), schizophrenia (176, 177) and autism spectrum disorder (178, 179). Alterations of the microbiota through stress and other prenatal or postnatal factors impacted the programming of the HPA axis in a sex-specific manner (82, 83, 150, 152).

Since early programming of the HPA-axis and immune system can be affected in a sex-specific manner by changes in maternal/offspring microbiota composition, a microbiota "hit" could program health and disease later in life.

8.0 Conclusion

Several decades after Barker first proposed the role of prenatal factors on health and disease later in life, his ideas have continued to be investigated and expanded upon. The microbiota community transmitted to the offspring may have plasticity – as other traits described in the Barker hypothesis. Dynamic changes in the maternal microbiota and the early offspring microbiota would occur due to pre- and postnatal environment respectively, as well as host genetics. Although these changes may be beneficial for immediate survival, they may result in immediate and later physiological and behavioral consequences. The microbiota act as a fourth

"hit", which interacts with the other factors to program for brain health and disease in later life. The microbiota is involved in mediating the effects of both postnatal and prenatal diet, drug exposure, and stress (see **Figure 3**).

This field has potential for the development of new bioactives, and dietary/lifestyle interventions that would modulate the microbiota during pregnancy to reduce the risk of disease later in life. Moreover, microbiome interventions may also influence maternal mental health as recently see with a placebo-controlled trial of a *Lactobacillus rhamnosus* during pregnancy and lactation (180). However, there are few studies directly assess the impact of changes to the microbiota composition in early life on brain health outcomes in adulthood. Further research should focus on identifying the interactions between these four "hits" as well as critical periods for microbiota modulation to support early neurodevelopment and brain health later in life. As this review shows, certain bacteria species are modified in response to developmental stimuli, future work is however, needed to understand if there is any convergence to such findings and understand their functional implications.

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Table 1. Prenatal and postnatal impact of drugs. This table summarizes the prenatal and postnatal impact of drugs on the microbiota, the gut, the brain and behavior from studies cited in this review.

Drug	Animal/ Model	Time of Exposure	Effect	Reference
Proton Pump Inhibitors	Humans	Postnatal	↑ incidence of *C. difficile* and other infections Change in gut microbiota composition and diversity ↑ in Bacteroidales order, *Streptococcus* genus ↓ Firmicutes	(42)
Metformin	Humans	Postnatal	Changes in gut microbiota composition and changes in some measures of diversity	(42)
Non-Steroidal Anti-Inflammatory Drugs	Humans	Postnatal	Distinct changes in microbiota composition allowing for prediction of changes to different types of drugs involved in overlapping intestinal development pathways	(42)
Opioids	Humans	Postnatal	↑ in alpha diversity, association with compositional distance ↑ Peptostreptococcaceae, ↓ *Parasutterella* ↑ Energy production and carbohydrate metabolism	(42)
Statins	Humans	Postnatal	Association with beta diversity Species level changes in composition	(42)
Antipsychotics	Humans	Postnatal	↓ alpha diversity, altered beta diversity ↑ Lachnospiraceae, ↓ *Akkermansia*	(42)
Antipsychotics: Risperidone	Human children	Early Postnatal	↑ Gut microbiota diversity ↑ Weight gain associated with *Clostridium* sp., *Lactobacillus* sp., *Ralstonia* sp. And Erysipelotrichacaceae family	(147)
Antipsychotics: Olanzapine	Female Rats	Postnatal	↑ Firmicutes to Bacteroidetes ratio, body weight ↓ Locomotor activity	(45)

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Antipsychotics: Olanzapine	Mice	Postnatal	↑ Body weight Effects dependent on gut microbiota ↑ Firmicutes to Bacteroidetes ratio	(146)
Anti-epileptic: valproic acid	Mice	Prenatal	↑ Firmicutes to Bacteroidetes ratio in offspring ↑ Caecal butyrate in male offspring Sex-specific impact	(44)
Anti-epileptic: valproic acid	Mice	Prenatal	↓ sensitivity to painful stimuli, ↑ sensitivity to non-painful stimuli in offspring ↓ Prepulse inhibition, social behavior, exploratory activity in offspring ↑ locomotor and repetitive/stereotypic-like hyperactivity in offspring	(65)
Anti-epileptic: valproic acid	Mice	Prenatal	↓ Exploratory activity and social interaction in offspring ↑ Interneuronal space in offspring ↑ Neuroinflammation and neuronal disorganization in offspring	(66)
Antibiotics: Succinyl Sulfa Thiazole	Female Rats	Prenatal	↓ Social interaction, exploration in elevated plus maze in offspring ↑ Anxiety in offspring Altered sensorimotor gating in offspring	(43)
Antibiotics combination: neomycin, bacitracin, pimaricin, acetic acid	Female mice	Prenatal	↓ Exploratory behavior with some persistence into postnatal weeks 7-8	(48)
Antibiotics: penicillin	Mice	Prenatal and Early Postnatal	↓ Anxiety-like behavior in male offspring ↓ Social behavior in offspring and social novelty ↑ Aggression, reduced social avoidance in offspring Differences in composition and diversity ↑ Brain cytokine expression ↓ Bacteroidetes, ↑ Firmicutes, Proteobacteria	(139)

Antibiotics: various – penicillin, vancomycin, or penicillin + vancomycin + chlortetracycline	Mice	Early Postnatal	↑ Adiposity ↑ Firmicutes to Bacteroidetes ratio, Lachnospiracaeae Shift in microbiota composition	(140)
Antibiotics: vancomycin or cocktail (pimaricin, bacitracin, neomycin)	Rats	Early Postnatal	Visceral hypersensitivity in males ↓ Transient receptor potential in cation channel subfamily V member 1, alpha-2A adrenergic receptor, cholecystokinin B receptor Changes in gut microbiota composition	(141)
Antibiotics	Humans	Early Postnatal	↓ Gut microbiota diversity noticeable after first year of life ↓ Gut microbiota stability Transient increase in antibiotic resistant genes	(137)
Antibiotics	Humans	Early Postnatal	↑ Risk of being overweight in later childhood in boys ↑ Adiposity in childhood	(138)
Antidepressant: Ketamine	Mouse (Chronic social-defeat stress)	Postnatal	Attenuated social-defeat stress specific decrease in Butyricimonas in susceptible mice Attenuated social-defeat stress specific increase in Deltaproteobacteria in susceptible mice	(54)
Antidepressant: Selective Serotonin Reuptake Inhibitors	Humans and Rodents	Prenatal	Change in gastrointestinal function, birth weight, metabolism, motor activity/development and weight in later life	(57)
Antidepressant: Selective Serotonin Reuptake Inhibitors	Mice	Early Postnatal	↓ Exploratory behavior ↑ Anxiety in elevated plus maze ↑ Latency in novelty suppressed feeding ↓ Shock avoidance	(144)
Antidepressant: Selective Serotonin Reuptake	Mice	Early Postnatal	↓ Exploratory behavior ↑ Depressive behavior in forced swim test and	(145)

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Inhibitors			sucrose preference test ↑ Latency in novelty suppressed feeding ↓ Shock avoidance	
Drugs of Abuse: Ethanol	Mice	Postnatal	↑ Gut permeability, bacterial growth in small intestine ↓ Operational taxonomic units of Firmicutes and ↑ in unknown bacteria, Verrucomicrobia, and Bacteroidetes in the caecum	(59)
Drugs of Abuse: Ethanol	Rats	Postnatal	Changes in colonic microbiota composition (reduction in richness, evenness, Shannon diversity)	(60)
Drugs of Abuse: Ethanol	Mice	Postnatal	↑ *Alistepes* genus, ↓ Clostridium and alpha diversity Similar changes previously associated with inflammation	(61)
Drugs of Abuse: Cocaine	Mice	Postnatal	Intestinal depletion of bacteria enhances behavioral responses of cocaine Short chain fatty acids can modulate cocaine responses	(62)

Table 2. Impact of unhealthy maternal or adolescent diet. This table summarizes the effects of unhealthy prenatal and postnatal diet on the microbiota, gut, brain and behavior from studies cited in this review.

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Diet	Model	Treatment Start Time	Effect of Diet	Reference
Maternal high-fat diet (36% kcal from fat)	Non-human primate	Before mating	↓ Spirochetes (*Treponoma spp* and *Sporobacter termitidis*) which are involved in carbohydrate metabolism ↓ *Campylobacter* in mother and offspring	(74)
Western Diet	Mice	4 weeks old	Compositional gut microbiota changes ↑ Firmicutes/Bacteroidetes Ratio ↑ Fat when microbiota transplanted into germ-free mice	(149)
Maternal Western diet	Mice	6 weeks before mating	↑ Firmicutes/Bacteroidetes ratio ↓ Sex-specific differences in colonic gene expression involved in overlapping intestinal development pathways	(75)
High-fat diet (45% kcal from fat)	Male Rats	4 weeks old	↑ Verrucomicrobia and Desulfovibrionaceae ↑ Energy production and carbohydrate metabolism	(72)
Maternal high-fat diet (60% kcal from fat)	Male Mice (7-12wks)	8 weeks before mating	↑ Social deficits, mediated by microbiota composition changes ↓ Microbiota diversity in mother and offspring	(73)
Maternal high-fat diet (60% kcal from fat)	Mouse	12-14 week diet before mating	Sex specific differences in gene expression and pathways	(77)
Maternal high-fat diet (60% kcal from fat)	Mouse	7 weeks before mating	↑ Nurr77 expression in males ↓ Exploration for novel object recognition in males	(78)

Maternal high-fat diet (60% kcal from fat)	Adult mice	Start of pregnancy	Abnormal hypothalamic gene expression No response to lipopolysaccharide Impaired post-stress response	(79)
Maternal Western diet	Neonatal mice	2 weeks before mating	Toll-like receptor 2/4 mediated toxicity in neonate from breast milk	(80)
High-fat diet (45% kcal from fat)	Mouse	Post weaning	↑ adrenal gland weight in females/↓ in males ↑ plasma corticosterone, glucocorticoid receptor levels in hypothalamus in females Sexually dimorphic effects in behavioral tests	(150)
High-fat diet (60% kcal from fat)	Male rats	Juvenile	↓ Spatial memory ↑ response to lipopolysaccharide-induced cytokines in hippocampus	(151)
High-fat diet (45% kcal from fat)	Male mice	Binge eating during adolescence	↑ Anxiety, cocaine self-administration in adulthood ↑ Corticosterone during withdrawal ↓ CB1, MOR expression in Nucleus Accumbens ↑ GHSR in Ventral Tegmental Area	(152)
High trans-fatty acids	Rats	Gestational exposure	↑ Serum endotoxins, hypothalamic cytokines in adulthood ↑ Hypothalamic inflammation via NFκBp65 in adulthood	(76)

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Figure Captions

Figure 1. Four "hits" programming for brain health and disease. In addition to the three "hits" posited by Barker (prenatal and postnatal environment, genetic predisposition), we propose that the microbiota acts a fourth "hit". The human microbiota is both influenced by and is also able to influence the other three factors. Together, these four "hits" can program for brain health and disease later in life.

Figure 2. Overlap of critical periods in neurodevelopment with alterations in microbiota diversity. Maternal vaginal and intestinal microbiota diversity increases over the course of pregnancy, concurrently with cell birth and migration, as well as apoptosis. After birth, microbiota diversity has been measured to increase throughout infanthood.

Figure 3. Prenatal and postnatal factors contribute to sex-specific programming of health in later life. The gut and vaginal microbiome of the mother is altered by diet, drugs, infection and stress. If birth occurs through vaginal delivery, the maternal vaginal microbiota colonizes the newborn's gut. If Caesarean delivery occurs, the maternal skin microbiome colonizes the infant gut. Early in life, diet drugs and stress can also impact the infant microbiota composition. The microbiota is important for sex-specific microglial maturation, which is responsible for the neuroinflammatory response. The hypothalamic-pituitary-adrenal (HPA) axis is also influenced by and can influence the gut microbiota. Normally, it can attenuate the inflammatory response from the microglia. These four "hits" could affect this axis and affect brain health in later life. There are also other factors in adulthood that can impact brain health and disease (i.e. environment, disease, stress and sex).

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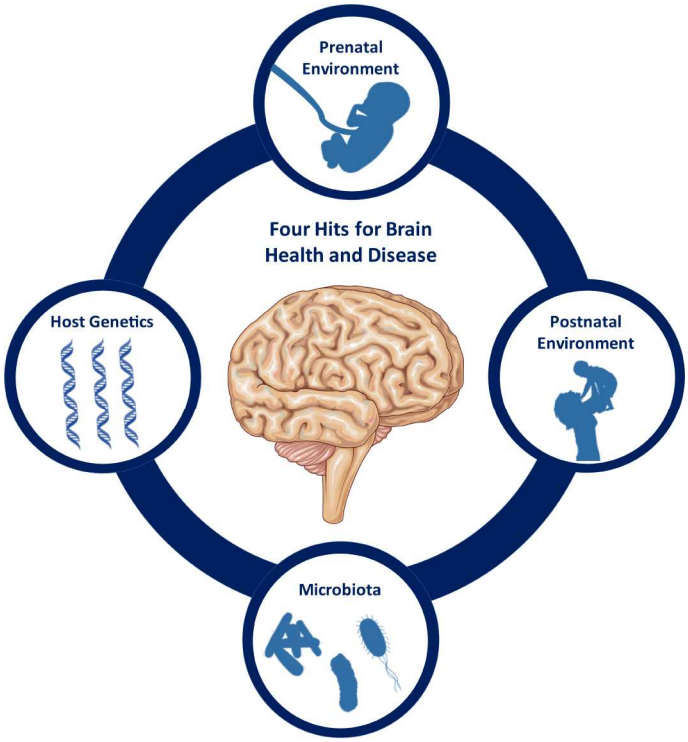

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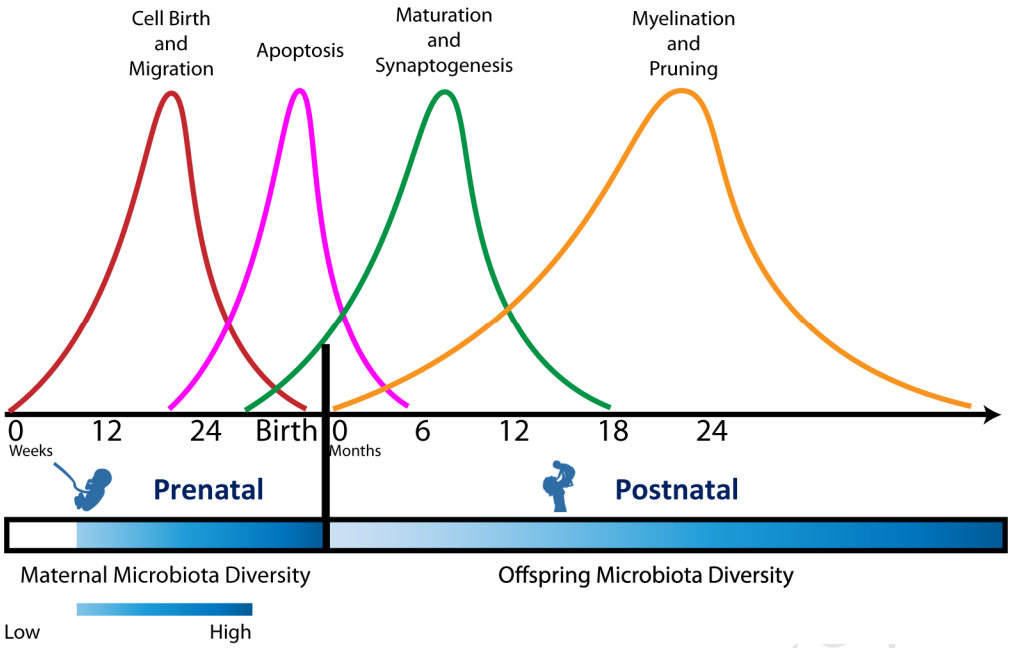

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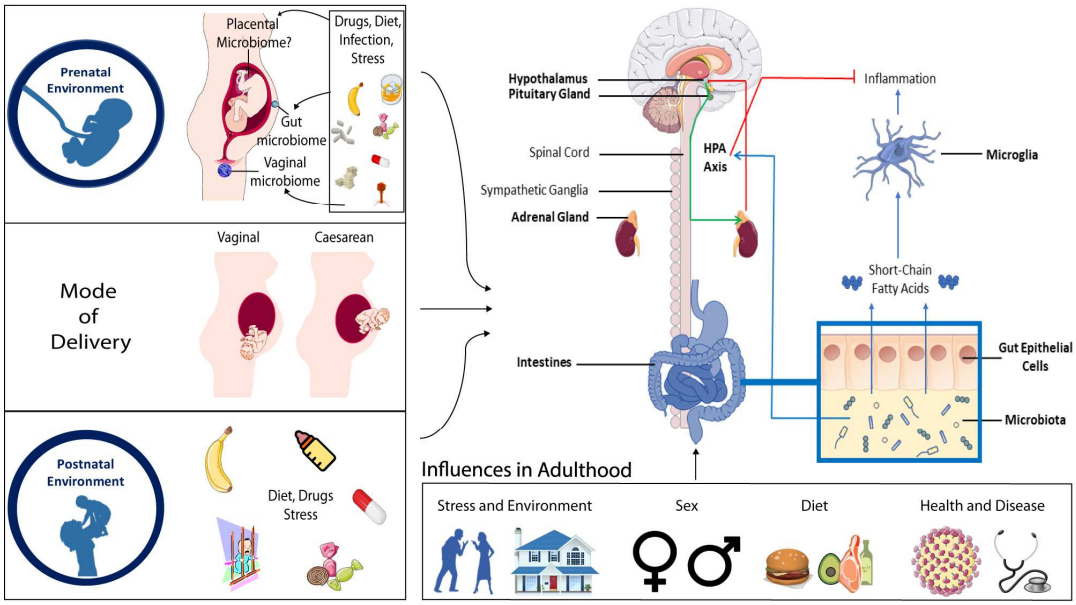

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